Appeal No. 05-1184
(Serial No. 09/674,002)

In the

United States Court of Appeals

for the

Federal Circuit

IN RE MARTIN BILLGER and MIKAEL BRULLS

Appeal from the United States Patent and Trademark Office,
Board of Patent Appeals and Interferences.

REPLY BRIEF OF APPELLANTS MARTIN BILLGER & MIKAEL BRULLS

COURTENAY C. BRINCKERHOFF
STEPHEN A. BENT
MICHELE M. SIMKIN
FOLEY & LARDNER LLP
3000 K Street, N.W., Suite 500
Washington, DC 20007
(202) 672-5300
Attorneys for Appellants

Of Counsel:
BARTON W. GIDDINGS
NPS PHARMACEUTICALS, INC.

MAY 31, 2005

COUNSEL PRESS, LLC (202) 783-7288 * (888) 277-3259

CORRECTED

CERTIFICATE OF INTEREST

Counsel for Appellants Martin Billger and Mikael Brulls certifies the following:

1. The full name of every party represented by me is:

   Martin Billger

   Mikael Brulls

   NPS Allelix Corp.

2. The name of the real party in interest represented by me is:

   NPS Allelix Corp.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   NPS Pharmaceuticals, Inc.

   NPS Allelix Corp.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

   Foley & Lardner LLP
   Courtenay C. Brinckerhoff, Esq.
   Stephen A. Bent, Esq.
   Michele M. Simkin, Esq.
   Barton W. Giddings, Esq.

May 31, 2005

Courtenay C. Brinckerhoff

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Federal Cases

Statutes

I. SUMMARY OF THE ARGUMENT

The Board decision is not supported by substantial evidence, as the factual findings underpinning the Board decision are not supported by the record. Moreover, prior art erroneously disregarded by the Board teaches away from the claimed invention.

In arguing for the Board decision, the Director fails to consider the non-obviousness of the claimed PTH formulations as a whole. Rather, the Director improperly focuses on isolated aspects of the claimed invention. Moreover, the Director improperly ignores portions of the prior art that unequivocally teach away from the claimed invention.

Like the Board, the Director completely disregards the teaching away of Martindale 1989 based only on its publication date. Both the Board and the Director arbitrarily characterize Martindale 1989 as "outdated" and ignore its teaching away without providing any evidence that its warning against using salt in liquid PTH formulations had been disproved as of the date of the invention. This is in contrast to Applicants, who provide evidence demonstrating that Martindale 1989's warning was still relevant at the time of filing, i.e., the similar warnings given in the '724 application.

In discussing the prior art, the Director mischaracterizes its teachings and cites selectively, improperly ignoring teachings that detract from the Board

decision. For example, the Director mischaracterizes Holthuis in alleging that this reference teaches that "most" prior art PTH formulations were reconstituted with saline. Moreover, the Director extends Endo beyond its teachings, inflating Endo's disclosure of lyophilized PTH preparations to encompass PTH formulations generally, and liquid preparations in particular. Furthermore, the Director erroneously alleges that Endo teaches the modification of Holthuis' PTH formulations. Like the Board, the Director alleges that Endo is more relevant to the present invention than the '724 application, even though it is only the '724 application, and not Endo, that addresses the stability of liquid PTH formulations [A87-88].

Finally, the Director improperly raises a number of new issues that are not part of the Board decision on appeal. This Court is charged with reviewing the Board decision, see, e.g. 28 U.S.C. § 1295(a)(4)(A), and should not entertain the Director's novel arguments.

II. ARGUMENT

The ultimate issue on appeal is whether the Board's decision of obviousness is supported by substantial evidence. Applicants show in their Appeal Brief and below that the Board decision cannot reasonably be reached from the evidence of record. The factual findings underlying the Board's obviousness decision are not supported by substantial evidence. See In re Zurko, 258 F.3d

1379, 1384 (Fed. Cir. 2001). Indeed, many of the Board's key findings are not supported by any evidence of record, and many are contradicted by the record.

Contrary to the arguments of the Director, this is not a case where the record reasonably supports inconsistent conclusions and the applicant merely disagrees with the conclusion reached by the Board. Instead, Applicants have identified specific factual findings of the Board that are not supported by the evidence of record, and have pointed to evidence of record – disregarded or ignored by the Board – that teaches away from the claimed invention, therefore warranting reversal of the obviousness decision. See, e.g., In re Haruna, 249 F.3d 1327, 1335 (Fed. Cir. 2001) (reversing an obviousness rejection where the art taught away from the invention). Because the record does not contain evidence sufficient to allow a reasonable fact finder to reach the Board's conclusions, the Board decision cannot be upheld. See In re Gartside, 293 F.3d 1305, 1312 (Fed. Cir. 2000).

A. THE DIRECTOR'S ARGUMENTS FAIL TO CONSIDER THE INVENTION AS A WHOLE AND FAIL TO CONSIDER ALL PRIOR ART TEACHINGS OF RECORD

The claimed invention relates to "stable, liquid pharmaceutical formulation[s]" that comprise: (i) a high PTH concentration (0.3-10 mg/ml); (ii) a buffer of pH 4 to 6; (iii) salt; (iv) mannitol; (v) a preservative; and (vi) water. [A1; A67]

The Director mischaracterizes the claimed invention as "involv[ing] the addition of 'salt' to parathyroid hormone ('PTH') compositions." See, e.g., Appellee Br. at 1. That characterization ignores significant aspects of the claimed invention, including: (i) a stable (ii) liquid (iii) high concentration PTH composition. This is important, as the prior art of record teaches away from an invention having the claimed combination of properties. In addition, the Director's arguments fail to consider all prior art teachings of record. Rather, the Director focuses on specific, selective passages that support the Board decision, and ignores statements that teach away or contradict the Board decision.

When all teachings of record are considered, the prior art clearly teaches away from the claimed invention. Specifically, the teaching most relevant at the time of the invention was Martindale 1989, which contains a clear and unequivocal warning to one of skill in the art to avoid the use of salt in liquid PTH formulations because it "cause[s] precipitation." Martindale 1989, pg. 1338, col. 1 [A122].

Endo reported that salt has a stabilizing effect on lyophilized (freeze-dried) PTH preparations comprising sugars, [A80] but Endo did not consider the effects of salt on liquid PTH formulations. Nor did Endo address the stability of its own lyophilized PTH preparations once reconstituted into liquid form. In fact, Endo's approach was criticized by the '724 application, which cautioned that "it has been

shown that this type of stabilization [utilizing salt] favours the formation of dimers." [A85]

Subsequent to Endo, Holthuis reported a lyophilized preparation of PTH that does not contain salt. [A76-77] Holthuis acknowledged that prior art PTH preparations had been made in different types of aqueous solutions, including saline and acidified water, but cites prior art noting problems with reconstituting in saline. [A75] Holthuis chose reconstitution with "sterile water" for its novel PTH preparations. [A75, 77]

Thus, at the time of the claimed invention, the prior art as a whole failed to suggest a stable, liquid, high concentration PTH formulation comprising salt, and indeed taught away from such a formulation. The prior art of record provided no reasonable expectation that such a liquid formulation would be stable, instead indicating that such a formulation would be subject to precipitation and dimerization.

B. THE BOARD'S DISREGARD OF MARTINDALE 1989 IS NOT SUPPORTED BY SUBSTANTIAL EVIDENCE

1. The Director Failed To Identify Any Evidence Supporting The Board's Finding That Martindale 1989's Teaching Away Was "Outdated" At The Time Of The Invention

A key error in this case is that the Examiner, the Board, and now the Director each disregarded a highly relevant prior art reference, Martindale 1989, based solely upon its publication date. No evidence has been proffered to

demonstrate the propriety of the Board's determination that the teaching away found in Martindale 1989 is erased from the state of the art because a later version of the reference, Martindale 1996, omits that teaching.

The Director refers to Martindale 1989 as "outdated," but cites absolutely no evidence of record supporting the Board's assumption that the absence in Martindale 1996 of the teaching away, admittedly found in Martindale 1989, reflected a change in the state of the art. Thus, the Board's disregard of Martindale 1989's teaching against the use of salt in liquid PTH formulations is not supported by substantial evidence, and should be reversed. See Lunsford, 357 F.2d at 389-390 (finding error where the Examiner ignored specific teachings without citing other references containing specific teachings demonstrating that the ignored teachings properly could be ignored); Zurko, 258 F.3d at 1386.

2. Applicants Provided Evidence That Revisions Evident In Martindale 1996 Do Not Reflect A Change In The Art

At page 22, the Director alleges that Applicants provided only "attorney argument" in support of their explanation for the revision to the PTH entry in Martindale 1996. This statement is false. Applicants cited the evidence found in the Preface of Martindale 1993, the intermediate edition of Martindale, which was

included in the addendum to Applicants' Brief.[1] This evidence was ignored by the Director.

As set forth at page 30 of Applicants' Brief, the Preface of Martindale 1993 explains that significant changes were made to "include a massive increase in information on proprietary medicines," and to reflect "a shift to a more clinical emphasis." As a result, the entry for PTH was shortened significantly from Martindale 1989 to Martindale 1993 and Martindale 1996. The editorial changes to the PTH entry are consistent with the explanation provided in the 1993 Preface.

The teaching away is not the only information absent from the revised versions of Martindale. As noted at page 29 of Applicants' Brief, entire sections of the PTH entry were removed, including the sections on "Units," "Adverse Effects and Precautions," "Absorption and Fate," and "Use and Administration."[2] Thus, the PTH entry shrank from 19 paragraphs in Martindale 1989 to only three paragraphs in Martindale 1993 and Martindale 1996.

---

[1] The Director has not questioned the Court's ability to take judicial notice of Martindale 1993 and has not argued against its consideration. See, e.g. Appellee Br. at 23 n.4.

[2] The Director notes that the "Osteoporosis" entry in Martindale 1996 includes information on the use of a PTH fragment (teriparatide) in the treatment of osteoporosis. Appellee Br. at 22. That does not discredit Applicants' point that valid information on the use of PTH to treat osteoporosis which was included in the Martindale 1989 PTH entry was omitted from the Martindale 1996 PTH entry.

The record contains no evidence that any of the omitted information was invalid or outdated when Martindale 1993 or Martindale 1996 were published. Instead, the only evidence of record on point, the explanation in the Preface of Martindale 1993, indicates that the changes to the PTH entry (including the omission of the teaching away), were part of wholesale editorial changes made to reflect a new focus of the reference. Thus, the Board's disregard of Martindale 1989's teaching away lacks evidentiary support, and should be reversed.

3. The Director's "Adverse Effects" Arguments Are Unsupported By Evidence And Contrary To Martindale

At pages 22-23, the Director makes its own attorney argument regarding the absence of the teaching away from Martindale 1996. The Director argues that the detrimental effects of salt on liquid PTH formulations would have been included in Martindale 1996 as an "adverse effect," but cannot support that argument with any evidence of record. Moreover, the Director's interpretation of an "adverse effect" as encompassing formulation characteristics, rather than relating to patient effects, is contrary to the conventional meaning of that phrase in pharmaceutical fields, and is inconsistent with its usage in Martindale 1996.

The PTH entry in Martindale 1989 further undermines the Director's arguments. That entry includes a section on "Adverse Effects and Precautions," [A122] but that is not where the teaching away from the use of salt in liquid PTH formulations is found. Instead, the teaching away is located at the beginning of the

entry, together with other information on PTH solutions. [A122] Given that Martindale 1989 did not include the teaching away in its "Adverse Effects" section, there is no support for the Director's assertion that the warning would have been included in Martindale 1996 as an "adverse effect."

4. The Young Case Cited By The Director Requires The Consideration Of All Evidence Of Record And Does Not Support The Board's Disregard Of Martindale 1989

The Director cites In re Young, 927 F.2d 588 (Fed. Cir. 1991), as confirming the Board's authority to weigh the teachings of apparently conflicting references. See, e.g., Appellee Br. at 23-25. However, nothing in Young permits the Board to do what it did here, which was to completely disregard a reference based only on its publication date. See, e.g., Board Decision at A6 (dismissing Martindale 1989 in favor of Martindale 1996 because of its later publication date). To the contrary, Young plainly states that "the Board must consider all disclosures of the prior art." 927 F.2d at 591 (emphasis added). See also In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998) ("The Board must consider all of the applicant's evidence."). Because the Board failed to follow that mandate here, its decision on obviousness should be reversed.

C. THE DIRECTOR MISCHARACTERIZED AND SELECTIVELY CITED THE PRIOR ART

1. Holthuis

a. Holthuis does not teach that "most" PTH formulations are reconstituted with salt water

The Director repeatedly mischaracterizes Holthuis by stating that the reference teaches that "most" freeze-dried PTH compositions are reconstituted using salt water. See, e.g., Appellee Br. at 16, 18, 26. The relevant portion of Holthuis is set forth below:

> PTH preparations . . . have been reconstituted from fresh or lyophilized hormone . . . . Most are prepared in water-based vehicles such as saline, or water acidified . . . to stabilize the hormone.

Col. 1., ln. 32-37. [A75] Thus, contrary to the Director's misleading characterization, Holthuis reports that most PTH preparations have been reconstituted with water-based vehicles. In no way does Holthuis indicate that saline was more commonly used than acidified water.

b. The Director ignores the impact on the skilled artisan of Holthuis' teaching of reconstitution with sterile water

While emphasizing statements in the Background section of Holthuis, the Director ignores its main teachings. This selective reading of the prior art is improper because a prior art reference must be considered "for all that it teaches." In re Fritch, 972 F.2d 1260, 1264 (Fed. Cir. 1992).

In the Fritch case cited by the Director at page 18, the Board's obviousness decision was reversed because the Board had focused on one aspect of a prior art device while ignoring another aspect that distinguished it from the claimed invention. Fritch, 972 F.2d at 1264-65. The Director's interpretation of Holthuis should be similarly rejected because the Director has focused on statements in the Background section of Holthuis while ignoring Holthuis' teaching of only "sterile water" to reconstitute its novel PTH formulations. See, e.g., Holthuis, col. 2, ln. 33-37; col. 5, ln. 24-28. [A75, 77]

The Director improperly combines statements from the "Background" section of Holthuis with statements from its "Summary of the Invention" section to allege that Holthuis teaches a PTH formulation that is reconstituted using "either salt water . . . or water." Appellee Br. at 6. A thorough reading of Holthuis reveals that the only liquid taught for reconstitution of Holthuis' novel PTH formulations is sterile water. Those skilled in the art, therefore, would not read Holthuis as "advocate[ing]" the use of saline for PTH reconstitution, as alleged by the Director, Appellee Br. at 20. Instead, one would understand from Holthuis that sterile water should be used for PTH reconstitution.

c. The only prior art liquid PTH formulation of record taught to be stable is Holthuis' salt-free PTH formulation

The Director ignores the fact that the only prior art liquid PTH formulation of record that is taught to be stable is Holthuis' salt-free PTH formulation. [A6]

The Director's position that Holthuis somehow provides motivation to ignore its teachings regarding reconstitution with sterile water and revert to a prior art reconstitution with saline is not supported by a fair reading of Holthuis. Moreover, the Director's position that someone skilled in the art reasonably would expect to be able to modify Holthuis in such a drastic fashion and still achieve a PTH formulation with the same stability properties as Holthuis' salt-free PTH formulation is not supported by any evidence of record. The warnings in Martindale 1989 and the '724 application that salt has detrimental effects on liquid PTH formulations make the Director's position unsustainable.

2. Endo

a. Endo does not teach that adding salt to the compositions taught by Holthuis is beneficial

The Director alleges throughout its Brief that Endo teaches the addition of salt to Holthuis' PTH compositions. See, e.g., Appellee Br. at 12, 17, 26. These assertions ignore both the relevant timing of Endo and Holthuis and significant differences between the compositions taught by Endo and Holthuis.

Endo is based on an application filed before Holthuis [A71, 79], and thus cannot literally teach that salt should be added to Holthuis' PTH compositions.

More significantly, Endo does not teach liquid, high concentration PTH formulations, nor does Endo teach the stability of such formulations. Low concentration PTH formulations are less likely to demonstrate the undesirable salt

side effects enumerated in Martindale 1989 and the '724 application, such as precipitation and dimerization.

As explained in Applicants' Brief at page 5, concentrated protein solutions were known to exhibit aggregation and precipitation, which are highly undesirable because they adversely affect both the available protein drug concentration and the physical and biopharmaceutical properties of the protein formulations. [A2; A157] Those skilled in the art therefore would not presume that Endo's teaching of increased stability in lyophilized PTH preparations would translate into increased stability of a liquid, high concentration PTH formulation.

b. Endo does not teach the benefits of adding salt to "PTH compositions" generally, but is limited to lyophilized preparations

The Director makes the same error as the Board, characterizing Endo as teaching that salt stabilizes "PTH compositions," see, e.g., Appellee Br. at 6-7, 17, 20, 24, and ignoring the fact that Endo teaches only that salt stabilizes lyophilized (freeze-dried) preparations of PTH.

Endo's focus on lyophilized preparations is evident from its own statement of the invention:

> It was unexpectedly discovered that dramatically improved stability for lyophilized preparations of PTH can be obtained by combining a

constant amount of sodium chloride with a sugar together before lyophilization.

Col. 1, ln. 30-34 [A80]. Because Endo is not concerned with liquid PTH preparations, Endo does not address the effects of salt on liquid PTH formulations, and does not indicate that its PTH preparations, once reconstituted, would be stable for any period of time. Thus, Endo simply cannot provide a suggestion or motivation to prepare a liquid, high concentration PTH formulation including salt with any reasonable expectation that the resulting formulation would be stable.

3. The '724 application

a. The '724 application is more relevant to the claimed invention than Endo

The Director did not respond to Applicants' showing that no substantial evidence supports the Board decision to give less weight to the '724 application than to Endo. See, e.g., Appellant Br. at 39-40. Instead, the Director simply repeated the Board's statement that because Endo teaches a PTH preparation comprising salt and mannitol it is more pertinent than the '724 application, which teaches a PTH preparation comprising salt and sucrose. Appellee Br. at 10. This statement is not supported by the record for at least two reasons.

First, this statement ignores the fact that Endo is directed to lyophilized PTH formulations [A75], while the '724 application teaches liquid PTH formulations. Moreover, it is only the '724 application that discusses the stability of liquid PTH

preparations. Like Martindale 1989, the '724 application teaches that the preparations should be "essentially free of chloride ions since [they] favour the formation of dimers." [A87-88] Those skilled in the art recognized that liquid formulations are subject to different problems than lyophilized preparations. See, e.g., Martindale 1989, at 1338. [A122] For example, liquid formulations are subject to precipitation, and it was known that the presence of water facilitates degradation reactions, such as oxidation.

Second, the Board's statement mischaracterizes Endo, as Endo is directed to PTH preparations comprising salt and sugar generally. Endo, col. 1, ln. 35-37. [A80]. Indeed, Endo teaches that sucrose is a preferred disaccharide for use in its formulations. Endo, col. 2, ln. 7-8. [A80] Thus, the mannitol/sucrose distinction drawn by the Board is a distinction without a difference.

Accordingly, there is no support for the Board's conclusion that those skilled in the art would consider Endo's teachings regarding the stability of lyophilized PTH preparations to be more relevant to the claimed stable, liquid PTH formulations than the teachings of the '724 application, which directly address the stability of liquid PTH formulations.[3]

---

[3] There also is no legal or factual basis for giving less weight to the '724 application because it "is just that, an application," as suggested at page 10 of the Director's Brief. As set forth in 35 U.S.C. § 102, any "printed publication" qualifies as prior art.

b. The Director failed to show that the Board's treatment of the '724 application was proper, and instead relies on Examiner arguments absent from the Board decision

In its discussion of the '724 application, the Director cites heavily from the Examiner's Office Actions, see, e.g., Appellee Br. at 10, 24-25, but the cited findings of the Examiner were not cited or adopted by the Board and do not form part of the Board decision on appeal.

The Board's only explanations for discrediting the '724 application are (i) its erroneous finding that "Endo was able to achieve the results the ['724 application] cautions against", and (ii) its erroneous finding that Endo's use of mannitol where the '724 application used sugar made Endo a "better" piece of prior art against the claimed invention. [A7-8] The explanations offered by the Director, including the alleged inadequacy of the experimental data set forth in the '724 application, do "not appear in the Board's decision and may not be the basis for affirmance." In re Thrift, 298 F.3d 1357, 1367 (Fed. Cir. 2002).

In any event, the Director's contention that "Example 7 [of the '724 application]. . . – the closest example to the teachings of Endo – shows no loss of PTH over a period of 1 or 3 months" (Appellee Br. at 25), misses the point of that example. Example 7 of the '724 application examines the stability of a PTH preparation that was made by dissolving PTH in water with sucrose and salt, and then lyophilizing the preparation. [A92] The resulting data show that a large

number of dimers were found in that preparation, as determined by SDS-PAGE analysis after three months. [A96] (Dimerization involves the coupling of PTH moieties, not degradation.) Thus, the reference correctly concludes from the data that "the addition of chloride ions has a negative effect on storage stability." [A91]

D. THE DIRECTOR IMPROPERLY RAISES NEW ISSUES

The Director's Brief raises a number of new issues that are not found in the Board decision on appeal, and that were not even raised by the Examiner during prosecution. The Director's attempts to distract this Court with new analysis, newly-minted theories, and new rationales undermine its credibility and beg the question whether the Director believes that the Board decision as issued should be sustained. See, e.g., In re Dembiczak, 175 F.3d 994, 1001 (Fed. Cir. 1999) (noting that the new analysis offered by the Commissioner "does little more than highlight the shortcomings of the [Board] decision"). As this Court is well-aware, the Board cannot be affirmed based on a ground of rejection or rationale that is not found in the Decision on appeal. Id.; see also Thrift, 298 F.3d at 1367.

1. The "Stable, Liquid" Claim Limitations Were Timely Submitted And Are Included In The Claims on Appeal

The Director repeatedly alludes to the timing of the amendment that added the "stable, liquid" limitations to the claims, and alleges that the amendment was somehow "belated." See, e.g., Appellee Br. at 10, 13, 28-30. This allegation is unfounded.

The claim amendments were timely submitted [A268-72] and were entered by the Examiner without dispute [A284-86]. The "Claims On Appeal" in Applicants' Appeal Brief before the Board included those limitations [A21-23, 33-36], were accepted by the Examiner in the Examiner's Answer [A37-39], and are identical to the claims on appeal before this Court [A67-70]. No statement in the Board decision comments on the timing of the claim amendments, or suggests that the amendments were improper.

2. Neither The Board Nor The Examiner Found The Invention Anticipated By The Prior Art, And The Record Evidence Does Not Support Such A Determination

Several statements in the Director's Brief suggest that the invention is anticipated by Holthuis and/or Endo. See, e.g., Appellee Br. at 19, 26, 28 n.6 & 30-31. The Board decision on appeal held the invention obvious [A9], and neither the Board nor the Examiner found the claimed invention to be anticipated or entered a 35 U.S.C. § 102 rejection. The Director's attempt to recast the issues on appeal by raising the specter of anticipation is improper, and is not supported by the evidence of record.

Neither Holthuis nor Endo teaches every aspect of the claimed invention, as required for a §102 rejection. The Board decision itself recognizes that Holthuis does not anticipate the invention: "'Holthuis fails to explicitly teach inclusion of sodium chloride (NaCl) in their pharmaceutical formulation.'" [A3] The Board's

reliance on Holthuis as the primary reference underscores Endo's failure to teach a number of aspects of the claimed invention. For example, Endo does not teach a stable, liquid, high concentration PTH formulation, as required by Applicants' claims.

The Director also refers to the prior art, saline-reconstituted PTH formulation referenced in the Background section of Holthuis, but that PTH formulation does not read on the claimed invention. There is no evidence that the cited PTH formulation was stable or contained: (i) a high PTH concentration, (ii) mannitol, (iii) a buffer, (iv) a preservative, and (v) salt, all of which are required by the claimed invention.[4]

The Director alleges that Applicants have not met their burden to distinguish the claimed invention from the prior art of record, because Applicants allegedly "never provided any evidence that the compositions disclosed in Endo . . . are not 'stable.'" Appellee Br. at 30. That allegation ignores direct evidence on point. As set forth above and in Applicants' Brief, both Martindale 1989 and the '724 application show that Endo's PTH formulations, once reconstituted, would be

---

[4] The Piazza reference, cited by the Director at page 20-21, provides no more relevant teachings than does the Background section of Holthuis. This reference was not cited by the Board and does not form part of the rejection on appeal. The Huston case, which the Director cites in footnote 3, page 21, does not give the Director carte blanche to cite any reference of record to support a Board decision, and the Director has not shown that its citation of Piazza is proper.

expected to be unstable because those references teach that liquid PTH formulations comprising salt are not stable. [A122; A85-88] Thus, Applicants indeed have shown that the claimed invention is neither anticipated nor rendered obvious by art of record.

3. Neither The Board Nor The Examiner Criticized The Scope Of Applicants' Examples

At pages 4 and 30, the Director criticizes the scope of Applicants' working examples as compared to the claimed invention. Neither the Board nor the Examiner raised any issue regarding Applicants' examples, or even remotely suggested that the claims are not adequately described or enabled by the specification. Thus, the Director's comments should not be given any weight.

Moreover, Applicants' patent application provides ample support for the claimed invention. For example, page 4, lines 3-11, teaches that the invention provides a liquid, high concentration PTH formulation that can be provided in a multidose formulation. [A159] Page 5, lines 15-31, teaches that the inventive formulations may include the other components that are recited in the claims (e.g., mannitol). [A160] The examples studying the stability of liquid PTH formulations under different conditions [A163-66] further demonstrate that the stability of the formulations was considered to be part of the invention.

In addition, the examples clearly and systematically demonstrate the feasibility and advantages of including the claimed components in a liquid PTH

formulation. Thus, Example 1 shows the feasibility and benefits of a high PTH concentration, Example 2 shows the benefits of using a buffer of pH 4 to 6, Example 4 shows the benefits of mannitol, Example 6 teaches the benefits of a preservative, and Examples 3-5 further show the advantages of formulations comprising salt. Thus, the examples as a whole plainly support the claimed PTH formulations.

III. CONCLUSION

For the reasons set forth in Applicants' Brief and above, the Board decision on appeal should be reversed.

Courtenay C. Brinckerhoff
FOLEY & LARDNER LLP
Attorney for Appellants

AFFIDAVIT OF SERVICE

United States Court of Appeals
for the Federal Circuit
No. 05-1184
----------)

IN RE MARTIN BILLGER and MIKAEL BRULLS

----------)

I, John C. Kruesi, Jr., being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

I am retained by Foley & Lardner LLP, attorneys for Appellants.

That on the **31nd Day of May 2005**, I served the within **Reply Brief of Appellants Martin Billger & Mikael Brulls** upon:

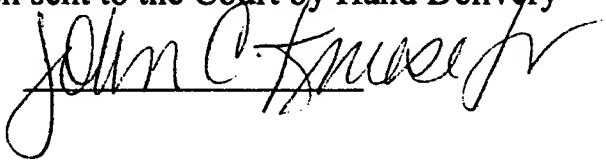
JOHN M. WHEALAN
LINDA M. ISACSON
HEATHER F. AUYANG
OFFICE OF THE SOLICITOR
P.O. Box 15667
Arlington, VA 22215
(571) 272-9035

Attorneys for Appellee

via Express Mail, by depositing 2 true copies of each, enclosed in a properly addressed wrapper, in an official depository of the USPS.

Unless otherwise noted, 12 copies have been sent to the Court by Hand Delivery

May 31, 2005



CERTIFICATE OF COMPLIANCE PURSUANT TO
FED. R. APP. P. 32(a)(7)(C) AND LOCAL RULE 32(b)

Counsel for the Appellants certifies the following:

Pursuant to Fed. R. App. P. 32 and Local Rule 32(b), the attached Reply Brief was printed using a proportionally spaced 14 point Times New Roman typeface and contains **4,613** words, as counted by Microsoft Word 2002.

May 31, 2005

Courtenay C. Brinckerhoff
Attorney for Appellants